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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
08/803,702	02/21/97	MAINO V	P-3639P1

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RICHARD J RODRICK
BECTON DICKINSON AND COMPANY
1 BECTON DRIVE
FRANKLIN LAKES NJ 07417-1880

EXAMINER	
EWOLDT,G	
ART UNIT	**PAPER NUMBER**
1644	24

DATE MAILED: 01/30/01

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No. 08/803,702	Applicant(s) Maino et al.
	Examiner Gerald Ewoldt	Group Art Unit 1644

☒ Responsive to communication(s) filed on 3/2/00 and 12/1/00 .

☐ This action is **FINAL**.

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire 3 month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) *19-55 and 61-63* is/are pending in the application.

Of the above, claim(s) *22, 34-38, 41, 42, 44, 46, and 48* is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *19-21, 23-33, 39, 40, 43, 45, 47, 49-55, and 61-63* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐approved ☐disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____ .

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____ .

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of References Cited, PTO-892

☒ Information Disclosure Statement(s), PTO-1449, Paper No(s). *18, 23*

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

DETAILED ACTION

1. The examiner of your application in the PTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Dr. Gerald R. Ewoldt, Group Art Unit 1644.

2. The request filed on 12/1/00 for a Continued Prosecution Application (CPA) under 37 CFR 1.53(d) based on parent Application No. 08/803,702 is acceptable and a CPA has been established. An action on the CPA follows.

3. Claims 19-21, 23-33, 39-40, 43, 45, 47, 49-55, and 61-63, are drawn to the elected species:
specific anti-cytokine antibody, anti-IFN-γ; the specific anti-T lymphocyte antibody, anti-CD4, the specific costimulus, anti-CD28 antibody; the specific viral antigen, cytomegalovirus (CMV), and are being acted upon.

4. In view of Applicant's amendment and declarations, filed 9/25/00, all previous rejections have been withdrawn.

5. The following is a quotation of the first paragraph of 35 U.S.C. § 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claims 19-21, 23-33, 39-40, 43, 45, 47, 49-55, and 61-63, are rejected under 35 U.S.C. § 112, first paragraph, as the specification does not contain a written description of the claimed invention, in that the disclosure does not reasonably convey to one skilled in the relevant art that the inventor(s) had possession of the claimed invention at the time the application was filed. This is a new matter rejection.

The specification and the claims as originally filed do not provide support for the invention as now claimed, specifically: an MHC-dependent nominal antigen.

Applicant's amendment, filed 3/12/99, asserts that no new matter has been added. However, the specification supports only the terms MHC directed T cell responses and nominal antigens. The amended term is not disclosed in the original specification or claims as filed.

7. Claims 19-21, 23-33, 39-40, 43, 45, 47, 49-55, and 61-63 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for:

a method of detecting antigen specific T lymphocytes, comprising: contacting a sample containing PBMC with an MHC-dependent nominal antigen and flow cytometrically detecting the intracellular binding of an anti-IL-2, anti-IFN-γ, or anti-TNF-α antibody, does not reasonably provide enablement for:

a method of detecting antigen specific T lymphocytes comprising: contacting a sample containing PBMC with an MHC-dependent nominal antigen and flow cytometrically detecting the intracellular binding of a cytokine-specific antibody.

The specification disclosure is insufficient to enable one skilled in the art to practice the invention as broadly claimed without an undue amount of experimentation. The scope of the claims is not commensurate with the enablement provided by the disclosure.

The specification discloses a method of intracellularly detecting only the cytokines IL-2, IFN-γ, or TNF-α. While antibodies for the detection of these and other secreted cytokines are well known in the art, the instant claims recite the detection of cytokines sequestered within T cells. Beckton Dickinson Application Note 1 (1996) teaches that the use of secretory inhibitors, such as BFA, may cause conformational changes to the proteins and thus "antibodies that work well in detecting secreted cytokines may perform poorly in intracellular assays". The reference therefore teaches that the use of any particular anti-cytokine antibody is unpredictable. Said unpredictability indicates that undue experimentation would be required to practice the invention as claimed in that, with the use of any given anti-cytokine antibody, there would be no particular expectation of success in the assay.

In re Wands, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988) indicates that the more unpredictable an area is, the more specific enablement is necessary in order to satisfy the statute. Thus, in view of the quantity of experimentation necessary, the lack of sufficient working examples, the unpredictability of the art, the lack of sufficient guidance in the specification, and the breadth of the claims, it would take undue trials and errors to practice the claimed invention.

The declaration under 37 CFR 1.132 filed 12/1/00 is insufficient to overcome the rejection of claims 19-21, 23-33, 39-40, 43, 45, 47, 49-55, and 61-63 based upon the first paragraph of 35 U.S.C. § 112 as set forth in the last Office

action because:

The declaration of Calman Prussin, M.D. is insufficient to demonstrate that it would not require undue experimentation to adapt the claimed method for the detection of other cytokines. Dr. Prussin, who's Curriculum Vitae indicates no particular training in cellular immunology and only one relevant peer-reviewed publication, merely asserts that the invention should work. The declaration is silent as to the differences between the conformations of secreted and intracellular cytokines, and is thus silent as to intracellular binding of anti-cytokine antibodies as relates to the claimed invention.

It is further noted that Applicant has previously submitted in Paper No. 10, filed 3/12/99, 1998 Becton Dickinson and PharMingen catalog entries indicating antibodies capable of binding intracellular cytokines. Regarding Exhibit A, indicating antibodies for use with the FastImmune™ Assay System, Applicant has not certified by appropriate declaration that the listed antibodies had been demonstrated to function in the claimed method at the time of the invention. Indeed, 3 of the 5 antibodies are marked **NEW**, thus indicating that said antibodies were not in the possession of Applicant at the time of the invention. Regarding Exhibit B, the antibodies in the 1998 PharMingen catalog, BD Application Note 23-5195-01 (page 7, column 2, June 2000) specifically states that the PharMingen antibodies have only been tested for use in a different method, not the claimed method, and that performance might be "altered" if used in the method of the instant claims.

8. Claims 19-21, 23-33, 40, 43, 45, 47, 49-55, and 61-63 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor, at the time the application was filed, had possession of the claimed invention.

There is insufficient written description to show that Applicant was in possession of "an inhibitor of cytokine secretion" (Claim 19), other than Brefeldin A (BFA). The specification discloses no definition for said inhibitor and teaches only the single species, BFA. Absent any definition, the claim must be read broadly to include any chemical that could inhibit cytokine secretion, presumably including toxins ranging from benzene to sodium azide. Thus, the specification fails to adequately define the claimed invention and one of skill in the art would conclude that the specification fails to disclose a representative number of species to describe the claimed genus. See *Eli Lilly*, 119 F.3d 1559, 43 USPQ2d 1398.

9. The instant application is Continuation in Part of Application No. 08/760,447 (12/6/96) and claims priority to said application. However, due to significant differences between the disclosures of the two applications, priority is denied. The '447 application discloses and claims a method for determining the antigen-specific activation of T cells. In contrast, the instant application discloses and claims a method of detecting individual T cells that respond specifically to an MHC-dependent nominal viral antigen. Note specifically that the '447 application discloses methods of assessing T cells within a population. Additionally, the priority document discloses no "MHC-dependent nominal viral antigens", as claimed in the instant application. Even the critical parameter, the length of the assay, is unclear in the parent application. While one figure indicates a 6 hour assay, the preferred embodiment (page 3) discloses a 101.5 hour incubation. Thus, priority to 08/760,447 is denied and the priority of the instant application is its filing date, 2/21/97.

10. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

11. Claims 19-21, 23-33, 39-40, 43, 45, 47, 49-55, and 61-63 are rejected under 35 U.S.C. 103(a) as being unpatentable Becton Dickinson Application Note 1, Detection of Intracellular Cytokines in Activated Lymphocytes (1996) in view of Maino et al. (FastImmune™ Assay System, 1995, IDS), and, U.S. Patent No. 6,143,299.

Application Note 1 teaches a method of detecting activated T lymphocytes in a whole blood sample, the method comprising: flow cytometrically detecting individual T lymphocytes after *in vitro* stimulation for no longer than 24 or no longer than 6 hours, including costimulation with an anti-CD28 antibody. Permeablized cells are treated with the inhibitor of cytokine secretion, BFA, and contacted with the T lymphocyte-distinguishing antibody, anti-CD4, the early activation marker, anti-CD69, and an intracellular cytokine specific antibody, anti-IFN-γ. The method further comprises the lysing of red blood cells and the addition of the chelator EDTA. The reference further teaches the use of various fluorophores, including FITC, PE, and PerCP, conjugated

to various antibodies to suit the particular assay (see entire document, particularly **Method**, pages 5-6).

The reference teaching differs from the claimed invention in that it does not teach activation with a CMV viral antigen.

Maino et al. teaches the use of viral antigens in the claimed method of detecting antigen specific T lymphocytes (see particularly page 4).

The '299 patent teaches a CMV viral antigen (see particularly column 19, line 60 - column 20, line 4). The reference further teaches said antigen would be useful because it derives from a known pathogen that causes a viral disease for which treatment would be desirable (see particularly column 19, lines 24-62).

From the teachings of the references it would have been *prima facie* obvious to perform a method of detecting activated T lymphocytes in a whole blood sample, the method comprising: flow cytometrically detecting individual T lymphocytes after *in vitro* stimulation for no longer than 24 or no longer than 6 hours, including costimulation with an anti-CD28 antibody. Permeablized cells are treated with the inhibitor of cytokine secretion, BFA, and contacted with the T lymphocyte-distinguishing antibody, anti-CD4, the early activation marker, anti-CD69, and an intracellular cytokine specific antibody, anti-IFN-γ, as taught by Application Note 1, using a viral activation antigen, as taught by Maino et al., specifically a CMV antigen, as taught by the '299 patent. One of ordinary skill in the art at the time the invention was made would have then been motivated to perform said method of detection using CMV specific T lymphocytes because CMV is a known pathogen that causes a viral disease for which treatment would be desirable, as taught by the '299 patent. Note that the substitution of various fluorophores such as FITC, PE, or PerCP, on various antibodies to suit the particular method is obvious and well within the purview of one of skill in the art.

12. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re*

Thorington, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1-8, 10-15, 17, 19, 24-36, and 39 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-8, 10-15, 17, 19, 23, 25-35 and 39 of copending Application No. 09/526,253. Although the conflicting claims are not identical, they are not patentably distinct from each other because both applications recite claims drawn to a method of detecting antigen-specific lymphocytes comprising flow cytometrically detecting a cytokine and a T cell subset in the presence of a protein synthesis inhibitor. Note that at the time of the restriction of the '702 application the claims of said application were drawn to a method of detecting antigen-specific cytokine production. Subsequent amendment of the claims of the '702 application has necessitated this rejection. Further note that the claims of the '702 application are drawn to "an MHC-dependent nominal antigen" while the claims of the '253 application are drawn to a "vaccine antigen". However, neither antigen is defined in the specifications and said antigens are not considered to be patentably distinct.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

13. No claim is allowed.

14. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Dr. Gerald Ewoldt whose telephone number is (703) 308-9805. The examiner can normally be reached Monday through Thursday from 8:00 am to 5:30 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (703) 308-3973. Any inquiry of a general nature or relating to the status of this application should be directed to the Technology Center 1600 receptionist whose telephone number is (703) 308-0196.

Papers related to this application may be submitted to Technology Center 1600 by facsimile transmission. Papers should be faxed to Technology Center 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 305-3014.

Patrick J. Nolan

G.R. Ewoldt, Ph.D.
Patent Examiner
Technology Center 1600
January 24, 2001

Patrick J. Nolan, Ph.D.
Primary Examiner
Technology Center 1600